Review / Derleme

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1090083

J Med Palliat Care 2022; 3(2): 117-121

Systemic sclerosis related interstitial lung disease and nintedanib

Sistemik skleroz ilişkili interstisyel akciğer hastalığı ve nintedanib

Nurhan Atilla[1], Gözde Yıldırım Çetin[2], Burak Okyar[2], Hüseyin Arpağ[3]

[1]Kahramanmaraş Sütçü İmam Üniversitesi, Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Kahramanmaraş, Türkiye
[2]Kahramanmaraş Sütçü İmam Üniversitesi, Tıp Fakültesi, Romatoloji Bilim Dalı, Kahramanmaraş, Türkiye
[3]Özel Batman Medical Park Hastanesi, Göğüs Hastalıkları Kliniği, Batman, Türkiye

Cite this article as / Bu makaleye atıf için: Atilla N, Yıldırım Çetin G, Okyar B, Arpağ H. Systemic sclerosis related interstitial lung disease and nintedanib. J Med Palliat Care 2022; 3(2): 117-121.

ABSTRACT

Although many mechanisms leading to lung fibrosis in systemic sclerosis-associated interstitial lung disease (SSc-ILD) have been suggested, this issue has not been fully understood yet. Recently, there has been increased evidence that the mediators and pathological mechanisms responsible for idiopathic pulmonary fibrosis (IPF) are similar to those in SSc-ILD. Accordingly, studies have been conducted to support that antifibrotic agents used in the treatment of IPF may also be useful in SSc-ILD. There are currently two antifibrotic agents on the market, namely nintedanib and pirfenidon. Although studies on the use of pirfenidone in SSc-ILD are not satisfactory, nintedanib studies have yielded positive results. The SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) study is the first and most comprehensive Phase III study on this subject. In 2019, the results of SENSCIS trial showed that, nintedanib significantly reduced the annual decline in lung function in SSc-ILD. After this trial, which did not include SSc-ILD patients with severe lung function loss, nintedanib licenced for the treatment of SSc-ILD worldwide. However, the currently available literature data lacks information about long-term effects and side effects of nintedanibe on SSc-ILD an also about the advanced SSc-ILD. The aim of this study is to review SSc-ILD patients treated with nintedanib, by also mentioning the pathogenesis of this disease according to the current literature.

Keywords: Sistemik skleroz, nintedanib, akciğer, fibrozis

ÖZ

Sistemik skleroz ile ilişkili interstisyel akciğer hastalığında (SSc-İAH) akciğer fibrozisine yol açan birçok mekanizma öne sürülmesine rağmen, bu konu henüz tam olarak anlaşılamamıştır. Son zamanlarda, idiyopatik pulmoner fibrozdan (İPF) sorumlu aracıların ve patolojik mekanizmaların SSc-İAH'dekilere benzer olduğuna dair kanıtlar artmıştır. Buna göre, İPF tedavisinde kullanılan antifibrotik ajanların SSc-İLD'de de faydalı olabileceğini destekleyen çalışmalar mevcuttur. Şu anda piyasada nintedanib ve pirfenidon olmak üzere iki antifibrotik ajan bulunmaktadır. SSc-İAH'de pirfenidon kullanımına ilişkin çalışmalar tatmin edici olmasa da, nintedanib çalışmaları olumlu sonuçlar vermiştir. SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) çalışması bu konudaki ilk ve en kapsamlı Faz III çalışmasıdır 2019'da SENSCIS çalışmasının sonuçları, nintedanib'in SSc-İAH'de akciğer fonksiyonundaki yıllık düşüşü önemli ölçüde azalttığını göstermiştir. Şiddetli akciğer fonksiyon kaybı olan SSc-İAH hastalarını içermeyen bu çalışmadan sonra, nintedanib dünya çapında SSc-İAH tedavisi için lisans almıştır. Bununla birlikte, şu anda mevcut olan literatür verileri, nintedanibin SSc-İAH üzerindeki uzun vadeli etkileri ve yan etkileri ve ayrıca ileri evre SSc-İAH üzerine etkilerinden yoksundur. Bu çalışmanın amacı, SSc-İAH'de nintedanib kullanımını güncel literatür eşliğinde, bu hastalığın patogenezinden de bahsederek gözden geçirmektir.

Anahtar Kelimeler: Sistemik skleroz, nintedanib, akciğer, fibrozis

INTRODUCTION

Systemic sclerosis (SSc) is a rarely seen connective tissue disease causing fibrosis of various internal organs, including kidneys, heart, lungs, musculoskeletal system and gastrointestinal tract and skin (1,2). Interstitial lung disease (ILD), develops in approximately 50% of patients within five years of being diagnosed with SSc (3). The high mortality rate is the reason, why many randomized controlled trials (RCTs) have been performed for the management of the disease in SSc-associated interstitial lung disease (SSc-ILD) patient group (4).

Evidence-based therapies used in clinical practice are immunomodulatory drugs such as mycophenolate mofetil (MMF) and cyclophosphamide (CYC) (4,5).

Corresponding Author / Sorumlu Yazar: Nurhan Atilla, Kahramanmaraş Sütçü İmam Üniversitesi, Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Kahramanmaraş, Türkiye
E-mail / E-posta: nurhanatillag@hotmail.com
Received / Geliş: 19.03.2022 **Accepted / Kabul:** 15.07.2022

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Despite immunomodulatory therapy, SSc-ILDs may show rapid deterioration of lung function, termed as 'progressive fibrotic phenotype'.

The widespread use of nintedanib to treat a similar fibrotic condition as idiopathic pulmonary fibrosis (IPF) has led to increased interest in exploring its role in SSc-ILD. The use of nintedanib treatment seems beneficial in this patient group resistant to immunomodulatory therapy.

Since the use of nintedanib in SSc-ILD is a current issue, we reviewed the literature on this subject. We searched in PubMed database to find relevant studies for our review. The literature search was conducted on March 12, 2022 and the keywords "systemic sclerosis AND scleroderma AND nintedanib were searched in titles and abstracts. First we found 35 results and the first study was published in 2015. Most of the articles were published after 2019. This is likely because the SENSCIS study was resulted in 2019. We selected 20 articles from the search results which were relevant to our review topic.

PATHOGENESIS OF FIBROSIS IN SSC-ILD

It is believed that, all ILDs are triggered by recurrent chronic vascular or epithelial injuries, or by granulomatous inflammation, which causing to cell destruction and in the case of fibrotic disease, to unregulated repair (6,7). Recurren micro-injuries causes damage of alveolar epithelium and basement membrane as a result cells in this area, causes the secretion of proinflammatory cytokines and chemokines such as TNF-α (tumor necrosis factor-alpha), IL-1 (interleukin-1) and MCP-1 (monocyte chemoattractant protein-1). These secreted mediators located in the interstitium or migrate here from the circulation activating other cells, especially fibroblasts, causes continued tissue damage (8,9). Fibroblasts are the keystone cells in fibrosing ILDs and attack the injury site from different areas.

DIFFERENCES OF PATHOGENESIS BETWEEN SSC-ILD AND IPF

Although pathogenesis of fibrosis basically similar in SSc-ILD and IPF, there are some differences. For example in SSc-ILD endothelium is the first to be damaged, while epithelial damage develops later. On the other hand, in IPF damage begins in the epithelium first. Immune dysregulation which develops following the epithelial and/or endothelial damage is, more prominent in SSc-ILD. In the last stage of pathogenesis, fibroblast activation and increased extracellular matrix production occurs in both IPF and SSc-ILD. Transformation of cells such as epithelium, endothelium, pericyte, adipocyte, into fibroblastic cells, and transformation of cells into myofibroblasts is similar in both diseases. MUC1 and KL-6 (Krebs von den Lungen-6) are markers of epithelial damage and correlate with the degree of lung fibrosis. The factors responsible for epithelial damage are genetic predisposition and environmental factors (smoking, aspiration, infections). The effect of smoking as a triggering agent in IPF is more pronounced, while, gastro-oesophageal reflux degree was associated with the degree of fibrosis in SSc-ILD. In pathogenesis, following epithelial and/or endothelial damage, the resulting immune dysregulation is more prominent in SSc-ILD. However, since the role of inflammatory cells in IPF is limited, inflammatory process active in SSc-ILD targeted therapies do not show efficacy in IPF.

Despite the fact that the pathophysiology mechanism of fibrosis in SSc-ILD is not well known, clinical trials have shown that nintedanib, an antifibrotic agent seems to inhibit this fibrotic process.

Nintedanib

Nintedanib is a potent inhibitor of intracellular tyrosine kinase and targets the Vascular endothelial growth factor (VEGF), Platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors (10). It was first used as a cancer drug. Because of its potential to slow down and perhaps inhibit the fibrosis process, it was studied to reduce respiratory pulmonary function decline, reduce exacerbations, and improve quality of life in patients with IPF (11). The pathophysiology of IPF causing pulmonary fibrosis is very similar to that of SSc-ILD.

In these diseases, fibrotic cascade begins with epithelial and/or endothelial cell damage and cell death (12). Also, the final common pathway causing lung fibrosis in IPF and SSc-ILD is believed to be occured by the recruitment and activation of myofibroblasts caused by aberrant transformation growth factor-beta (TGF-B) signaling (12). Consequently, myofibroblasts, which are specialized fibroblasts, cause fibrosis in both IPF and SSc-ILD through excessive extracellular matrix deposition (13).

Nintedanib experience in SSc-ILD: first case report

In 2018 the first case report demonstrating the clinical benefit of nintedanib in a patient with SSc-ILD published by Duarte et al. (14). This female patient was diagnosed with SSc at the age of 41 and ILD developed within seven years. Unfortunately, immunosuppressive agents could not prevent progression in lung fibrosis. Nintedanib treatment, which was only indicated for IPF at that time, was started at a dose of 2X150 mg/day with the consent of the patient. One year after starting nintedanib, the need for supplemental oxygen therapy was decreased, forced vital capacity (FVC) was slightly increased and the patient was clinically improved.

SENSCIS TRIAL: FIRST RANDOMIZED CLINICAL TRIAL IN SSC-ILD

In 2019 the results of the SENSCIS (ClinicalTrials.gov identifier: NCT02597933) trial were announced. This was a double-blinded, large-scale, phase III randomized clinical trial. A total of 576 patients (placebo 288, nintedanib 288) from 32 countries participated to this study. Fibrosis over 10% on high-resolution computed tomographic (HRCT) scan was accepted as ILD. Patients with mild or moderate ILD, whose diffusing lung capacity for carbon monoxide (DLCO) over than 30% and FVC was over than 40% of the predicted value were included to the study. The primary end-point of the trial was the yearly decline of FVC, which was assessed over 52 weeks. At the end of 52 weeks, the primary end-point analysis showed that the annual decline of FVC was 93.3 mL in placebo group and 52.4 mL in nintedanib group.

The most common adverse event in placebo and nintedanib group was non-severe diarrhea (75.7% vs 31.6%), that occurs within the first 3 months of treatment. Most patients were treated symptomatically, although some patients required temporary discontinuation and/or dose reduction of the drug. Elevations in aspartate aminotransferase, alanine aminotransferase level, to at least three times the upper limit of the normal range, were reported in 0.7% of patients in the placebo group and 4.9% of patients in the nintedanib group. There wasn't any difference between the placebo and nintedanib groups in terms of newly developing digital ulcers (DU). Because these results were statistically significant, nintedanib was approved as the first drug to slow the decline in respiratory function in SSc-ILD patients (15).

Subgroup Analyse of SENSCIS in Asians

In 2021 Azuma et al. (16) examined the subgroup analysis of the SENSCIS trial in Asian race. They compared the non-Asians (placebo 207, nintedanib 226) with Asians (placebo 81, nintedanib 62). FVC decline over 52 weeks was similar between non-Asian and Asian patients both in the placebo group, (-99.9 mL versus -90.6 mL) and in the nintedanib group (-39.0 mL vs - 44.3 mL). The most common side effect was diarrhea and was reported with similar frequency of non-Asians and Asians; in the placebo group (32.9% vs 28.4%) and nintedanib group (74.3% vs 80.6%).

As a result, this study also proved that, nintedanib showed significant benefit in slowing progression of SSc-ILD in non-Asians and Asians with a similar adverse event profile.

Subgroup Analyse of SENSCIS in Japanese

In 2021 Kuwanaa et al. (17) examined the subgroup analysis of the SENSCIS trial in Japanese patients with SSc-ILD. They compared the non-Japanese (placebo 252, nintedanib 254) with japanese (placebo 36, nintedanib 34). FVC decline over 52 weeks in Japanese patients was similar between placebo and nintedanib group (-90.9 mL versus -86.2 mL). For non-Japanese patients annual FVC decline in placebo group was higher than nintedanib group (-93.6 mL vs 47.9 mL). In the nintedanib group, asymptomatic liver enzym elevations were reported in 6 patients. Diarrhea was reported in 28 patients in the nintedanib group. But none of them were serious. In placebo group mild diarrhea reported in 11 patients. Although skin ulcers reported as adverse events were more frequent in the nintedanib group than in the placebo group (8 vs 3), the number of patients in each group were rare overall.

UNANSWERED QUESTIONS

Pneumothorax and Nintedanib

Pneumothorax has not been reported in SENSCIS trial. However, this clinical trial was conducted in patients with relatively good lung function. Data in the literatüre on the use of nintedanib in severe SSc ILD is insufficient. Sumi et al. (18) reported two patients with severe SSc-ILD, who developed spontaneous pneumothorax during nintedanib therapy. In a post-marketing survey in Japan, the frequency of pneumothorax in patients with IPF treated with nintedanib was low at 0.33% (17). Sumi et al (18) explained this situation as; fibrosis increases the fragility of the lungs, nintedanib, on the other hand, may increase fragility even more due to its anti-VEGF effect.

Digital Ulcer and Nintedanib

Although the pathophysiology of DU development in SSc is not known exactly, it is thought to result from decreased circulation due to the Raynaud phenomenon in distal areas like fingers. DU management is important in SSc as it can result in serious infections, gangrene and autoamputation. Currently available treatment is calcium channel blockers, antiaggregants, prostaglandin I2 (PGI2) analogues, endothelin receptor antagonists (ERA), phosphodiesterase-5 (PDE-5) inhibitors. Since SSc skin involvement occurs due to microvascular changes and fibrosis-related changes, long-term data are needed on the effect of nintedanib in skin involvement with DU.

In the SENSCIS study, no difference was found between nintedanib and placebo groups in terms of newly developing DU. But patients with more than three DU at baseline were excluded. There is not enough data in the current literature on the results of nintedanib use in patients with a large number of digital ulcers or severe skin involvement. Although there is general agreement that nintedanib can potentially impair angiogenesis and wound healing, more RCTs are needed in this area.

Nintedanib in Severe Progressive Fibrotic SSc-ILD

According to the extent of skin involvement in SSc, there are two clinical patterns, diffuse and limited. The diffuse pattern progresses more rapidly than the limited pattern, and its mortality is higher. Severe SSc-ILD is more common in diffuse pattern. Since the progression is rapid and mortality is high in this patient group, long-term follow-up is not possible. Therefore, the number of large case series published in this field is insufficient.

Bordas-Martinez et al. (19) hypothesized that patients with severe progressive fibrotic SSc- ILD (FVC <40% predicted or DLCO <30% of predicted) who are candidates for lung transplant may also benefit from nintedanib therapy. In this limited series of 4 cases with progressive fibrosing SSc- ILD, patients were treated with mycophenolate (2x720 mg/day) and nintedanib (2x150 mg/day). However, three of them also received corticosteroids less than 10 mg/day. Long-term oxygen therapy was started in one patient just before antifibrotic therapy. In two patients, a significant FVC improvement was observed, and in other two DLCO and FVC decline slowed down. Three patients reported digestive system complaints, 1/4 asthenia, 1/4 presented liver function elevation and 2/4 weight loss. All adverse events that developed were mild and none of the patients discontinued treatment for this reason. Lung transplantation was performed in one patient 249 days after the start of antifibrotic therapy.

300 mg/day or 200 mg/day?

The standard treatment dose of Nintedanib is 300mg/day. The level of efficacy at doses lower than the standard treatment dose is not exactly known.

Nishino et al. (20) reported a 73-year-old female patient with a diagnosis of SSc-ILD who had significant improvement in HRCT images following nintedanib treatment. Due to increase in ground glass areas on HRCT 26 months after the first visit, and deterioration in general condition, nintedanib was started as 2×100 mg/day. At the first month of nintedanib treatment, the patient reported an improvement in her dyspnea and cough. There were no side effects such as nausea or loss of appetite. Diarrhea did not develop, but the patient was using codeine phosphate as an antitussive. In the HRCT performed at the eighth month of nintedanib treatment, it was determined that the ground glass opacities significantly regressed. Radiological regression on HRCT was accompanied by a decline in dyspnea on exertion and dry cough. This case report is very meaningful as it shows that there is significant radiological improvement after the initiation of 200 mg/day nintedanib treatment.

Respiratory Tract Infection

The development of pneumonia was reported as a serious adverse event in the SENSCIS study. Pneumonia was much less common in the placebo group compared to the nintedanib group (0.3% vs 2.8%) (15). In patients with advanced ILD, concomitant use of mycophenolate and/or corticosteroids, clearly increases the incidence of pneumonia. A potential risk of infection due to the effect of nintedanib on macrophage function remained unanswered.

CONCLUSION

Clinical studies have proven that nintedanib has clinical benefits in the management of SSc-ILD. On the other hand, there is a need for long-term case-control series in this area. We hope that in the near future a large number of case series including nintedanib experiences in advanced SSc-ILD and the effects and side effects in SSc-ILD patients treated with nintedanib will be published.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Denton CP, Khanna DK. Systemic sclerosis. Lancet 2017; 390: 1685-99.
2. Kafle S, Magar MT, Patel P, Poudel A, Cancarevic I. Systemic sclerosis associated interstitial lung disease and nintedanib: a rare disease and a promising drug. Cureus 2021; 13: 16404.
3. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017; 76: 1897-905.
4. Roofeh D, Distler O, Allanore Y, Denton CP, Khanna D. Treatment of systemic sclerosis-associated interstitial lung disease: lessons from clinical trials. J Scleroderma Relat Disord 2020; 5: 61-71.
5. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006; 354: 2655-66.
6. Strieter RM, Mehrad B. New mechanisms of pulmonary fibrosis. Chest 2009; 136: 1364-70.
7. Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. Lancet 2012; 380: 680-8.
8. Mathai SK, Gulati M, Peng X, et al. Circulating monocytes from systemic sclerosis patients with interstitial lung disease show an enhanced profibrotic phenotype. Lab Invest 2010; 90: 812-23.
9. Huang X, Yang N, Fiore VF, et al. Matrix stiffness-induced myofibroblast differentiation is mediated by intrinsic mechanotransduction. Am J Respir Cell Mol Biol 2012; 47: 340-8.
10. Roth GJ, Binder R, Colbatzky F, et al. Cancer Res 2008; 68: 4774-83.

11. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011; 365: 1079-87.

12. Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis Rheumatol 2014; 66: 1967-78.

13. Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. Eur Respir Rev 2015; 24: 102-14.

14. Duarte AC, Santos MJ, Cordeiro A. Anti-fibrotic nintedanib-a new opportunity for systemic sclerosis patients? Clin Rheumatol 2018; 37: 1123-7.

15. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis 2020; 79: 1478-84.

16. Azuma A, Chung L, Behera D, et al. Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. Respir Investig 2021; 59: 252-9.

17. Kuwana M, Ogura T, Makino S, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: a Japanese population analysis of the SENSCIS trial. Modern Rheu J 2021; 31: 141-50.

18. Sumi T, Uehara H, Tada M, et al. Spontaneous pneumothorax during nintedanib therapy in patients with systemic sclerosis-associated interstitial lung disease. Respirology Case Reports 2021; 9: 1-4.

19. Bordas-Martinez J, Llanos-González AB, Jodar-Masanes R. Experience with nintedanib in severe pulmonary fibrosis associated with systemic sclerosis: a case Series. Open Respiratory Archives J 2021; 3: 1-3.

20. Nishino K, Sasatani Y, Ohara G, Kagohashi K, Satoh H. Nintedanib-mediated improvement in CT imaging in pulmonary fibrosis associated with systemic scleroderma. Adv Respir Med 2021; 89: 528-31.